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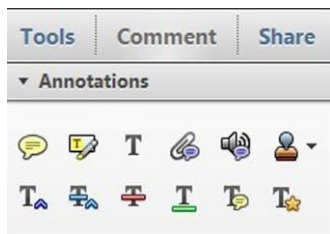


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# Left ventricular rotational abnormalities in hemophilia—insights from the three-dimensional speckle-tracking echocardiographic MAGYAR-Path Study

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**Contributions:** (I) Conception and design: A Nemes; (II) Administrative support: N Ambrus; (III) Provision of study materials or patients: A Nemes, Á Kormányos, P Domsik, N Gyenes; (IV) Collection and assembly of data: Á Kormányos, K Vezendi, I Marton, Z Borbényi; (V) Data analysis and interpretation: Á Kormányos; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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**Background:** Hemophilia is an X-linked inherited disorder primarily affecting males, its major types are type A (deficiency in factor VIII) and B (deficiency in factor IX), and is considered to be the most common severe congenital coagulation factor deficiency. The present study was designed to test whether any differences in left ventricular (LV) rotational mechanics could be demonstrated between male patients with hemophilia and healthy controls using three-dimensional speckle-tracking echocardiography (3DSTE)-derived virtual LV model.

**Methods:** The present study consisted of 17 patients with hemophilia, however, 3 patients were excluded due to insufficient image quality. In the remaining patient population, 12 patients had hemophilia A and 2 patients had hemophilia B (mean age: 42.2±18.9 years, all males). The control group comprised 16 age-matched healthy subjects (46.0±5.9 years, all males).

**Results:** None of the routine two-dimensional echocardiographic data differ between patients with hemophilia and controls. None of the patients and controls showed ≥ grade 1 valvular regurgitations and had valvular stenoses. In one subject, the near absence of LV twist called as LV “rigid body rotation” could be detected, data of which were managed separately. While 3DSTE-derived apical LV rotation was 3.65 degrees, basal LV rotation proved to be 3.57 degrees leading to 0.08-degree LV apico-basal gradient suggesting counterclockwise LV “rigid body rotation”. In the remaining patients, both LV apical rotation (7.25±6.20 vs. 10.07±3.92 degrees, P<0.02) and LV twist (10.24±5.60 vs. 14.41±4.26 degrees, P<0.003) showed significant impairment in patients with hemophilia.

**Conclusions:** LV rotational abnormalities are present in hemophilia with reduced LV apical rotation and twist.

**Keywords:** Three-dimensional (3D); speckle-tracking; echocardiography; hemophilia; left ventricular (LV); rotation; twist

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## Introduction

Hemophilia is an X-linked inherited disorder primarily affecting males, its major types are type A (deficiency in factor VIII) and B (deficiency in factor IX) and is considered to be the most common severe congenital coagulation factor deficiency (1). Its estimated prevalence is 17.1 cases/100,000 males for all severities of hemophilia A and 3.8 cases/100,000 males for all severities of hemophilia B (2). Together with atrial fibrillation, there is a possible higher risk for coronary artery disease (CAD) in hemophilia and its incidence is increasing due to the fact that life expectancy of hemophilia patients approximates that of the general population (3,4). However, CAD mortality in hemophilia is lower compared to that of the general population possibly due to the protective effect on thrombus formation of the existing hypocoagulable state (4). Outcome of treatment for cardiovascular disease is similar to that in the general population in hemophilia (5). Moreover, no differences in cardiovascular comorbidities and their earlier onset could be demonstrated in hemophilia A compared to controls (6). Although lot of facts are known about cardiovascular diseases and the risk in hemophilia, no clinical data are available about hemophilia related potential changes in myocardial mechanics.

Myocardial mechanics is highly dependent not only on cellular dysfunction, but also on left ventricular (LV) hypertrophy, fibrosis and wall stress (7). Haemostatic mechanisms are altered in haemophilia, which plays a major role in maintaining the structural and functional integrity of the vascular system, theoretically having effects on myocardial mechanics as well via changing wall stress (shear stress) (8). In all disorders in which any of these parameters are affected, theoretically myocardial mechanics could change. LV rotational mechanics is an important part of the LV pumping function showing early alterations in several disorders (9,10). Three-dimensional (3D) speckle-tracking echocardiography (3DSTE) is a new clinical tool with the ability of non-invasive analysis of LV rotational mechanics using digitally acquired 3D “echocloud” to create a virtual cast of the LV (11). The present study was designed to test whether any differences in LV rotational mechanics could be demonstrated between male patients with hemophilia and healthy controls using 3DSTE-derived virtual LV model.

## Methods

### Patient population

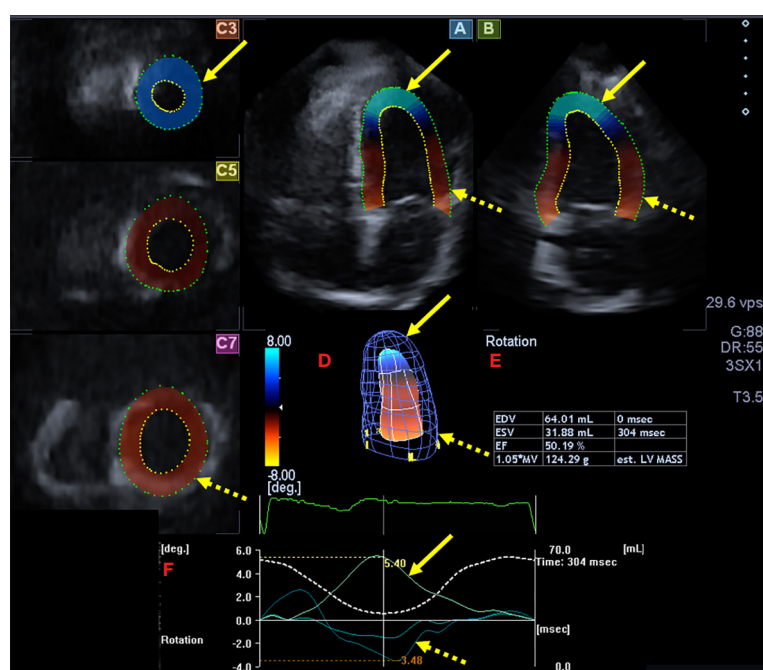
The present study consisted of 17 patients with hemophilia,

who were recruited on voluntary bases prospectively from the outpatient clinic of our tertiary Hematology Division, Department of Medicine, University of Szeged, Hungary. None of them had any known cardiovascular disorder. Due to insufficient image quality, 3 patients with hemophilia were excluded. In the remaining 14 patient population, 12 patients had hemophilia A and 2 patients had hemophilia B (mean age:  $42.2 \pm 18.9$  years, all males). From cardiovascular risk factors, 6 patients had hypertension, 4 patient showed hyperlipidaemia and 2 subjects had type 2 diabetes mellitus. Two patients were obese, smoking was present in 2 cases. All above mentioned risk factors were managed with mono- or combined therapy. Although none of the subjects had any known cardiovascular disease, hepatitis C virus (HCV) positivity was present in 10 subjects and hemophilic arthropathy was diagnosed in 8 patients. Diagnosis was established in infant age in all cases. Symptoms were mild in 7 cases and severe in 10 subjects. Factor level was below 1% in 9 cases and 4% in 2 cases, 6% in 1 case, 8% in 1 case, 9% in 2 cases, 10% in 1 case, 29% in 1 case, respectively. Therapy was based on demand in 9 patients and was prophylactic in 9 subjects. The mean dose of factors was between 1,000–6,000 U/week for each patient. The control group comprised 16 age-matched healthy subjects ( $46.0 \pm 5.9$  years, all males). A subject was considered to be healthy, if he/she had no symptoms or cardiovascular risk factors, no history of chronic disease or medication use, had a negative physiological examination and routine electrocardiography (ECG) and echocardiography showing normal results.

Complete two-dimensional (2D) Doppler echocardiographic examination and 3DSTE were performed in all patients with hemophilia and controls by the same sonographer (ÁK). The presented work is a part of the Motion Analysis of the heart and Great vessels by three-dimensional speckle-tracking echocardiography in Pathological cases (MAGYAR-Path) Study, which aimed to assess diagnostic and prognostic value of 3DSTE-derived LV rotational parameters among others in different disorders including hemophilia (“magyar” means “Hungarian” in Hungarian language). The local institutional ethical committee approved the study, which complied with the ethical guidelines set in the 1975 Declaration of Helsinki (and updated versions) and all patients and controls gave informed consent.

### 2D Doppler echocardiography

Routine echocardiography was performed using a Toshiba



**Figure 1** Analysis of a three-dimensional (3D) echocardiographic dataset: apical four-chamber view (A), apical two-chamber view (B) and apical (C3), mid-ventricular (C5), and basal LV (C7) short-axis views. A virtual 3D cast of the LV (red D), LV volumetric data respecting the cardiac cycle (red E), LV rotational curves (lines) and time-LV volume changes (dashed line) during the cardiac cycle (red F) are presented in a hemophilia patient with normal directions of LV rotational curves. Yellow arrow indicates maximum counterclockwise LV apical rotation, while dashed yellow arrow indicates maximum clockwise LV basal rotation. LV, left ventricle; EDV, end-diastolic volume; ESV, end-systolic volume; EF, ejection fraction.

Artida<sup>TM</sup> echocardiography device (Toshiba Medical Systems, Tokyo, Japan). 2D grayscale harmonic images were acquired with a broadband 1–5 MHz PST-30SBP phased-array transducer positioned in the left lateral position. Chamber quantification and LV ejection fraction (LVEF) measurements were performed in accordance with the guidelines. Relative wall thickness was measured as: interventricular septum (IVS) thickness + posterior wall (PW) thickness divided by LV diastolic diameter (12). Potential valvular heart diseases were evaluated with Doppler echocardiography.

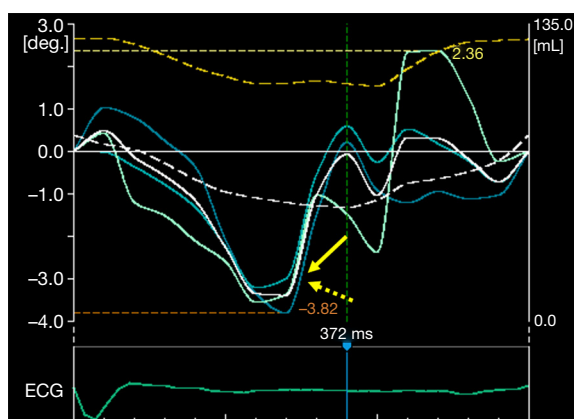
### 3DSTE

The same Toshiba Artida<sup>TM</sup> echocardiography device (Toshiba Medical Systems, Tokyo, Japan) equipped with a PST-25SX matrix-array transducer (Toshiba Medical Systems, Tokyo, Japan) with 3D capability was used for measurements (7). The apical window was used to acquire six wedge-shaped sub-volumes during a single

breath-hold to create full volume 3D datasets. 3D Wall Motion Tracking software version 2.7 (Toshiba Medical Systems, Tokyo, Japan) was used for offline analysis of data. The software automatically selected several long- and short-axis views at end-diastole from the 3D datasets acquired digitally. Regional LV rotations were defined as circumferential rotation around the long-axis of apical and basal segments of the LV during systole (in degrees). LV rotational mechanics were evaluated by the measurement of the following parameters (Figure 1) (11,13):

- ❖ LV basal (defined as the degree of clockwise rotation of LV basal myocardial segments) and apical (defined as the degree of counter-clockwise rotation of LV apical myocardial segments) rotation;
- ❖ LV twist (defined as the net difference between LV basal and apical rotation);
- ❖ Time to peak degree of LW twist from the start of the cardiac cycle;
- ❖ If apical and basal LV rotations were in the same





**Figure 2** Demonstration of LV rotational curves in a hemophilia patient with LV “rigid body rotation”. All curves are in the same clockwise direction within almost the same amplitude. Yellow arrow indicates maximum (reversed) clockwise LV apical rotation, while dashed yellow arrow indicates maximum clockwise LV basal rotation.

clockwise or counterclockwise direction (which phenomenon is called as LV “rigid body rotation”, LV-RBR), only LV apico-basal gradient could be calculated (maximum LV apical rotation minus maximum LV basal rotation) due to absence of LV twisting mechanics (*Figure 2*) (13,14). Using the same 3D LV cast, LV longitudinal strain, the most frequently used LV strain parameter was also calculated.

### Statistical analysis

Variables were presented as mean  $\pm$  standard deviation or frequencies and percentages (%). Normality of distribution was assessed by Shapiro-Wilks test, while homogeneity of variances was tested by Levene’s test. In case of normally distributed datasets, Student’s *t*-test was performed, in case of not-normally distributed datasets, Mann-Whitney Wilcoxon test was used. GPower 3.1.9 Software (Heinrich-Heine Universität, Düsseldorf, Germany) was used to calculate power: in the presence of effect size: 0.8, alpha: 0.04, power: 0.8, the minimum group size is  $n=13$ . Intraobserver and interobserver variability were assessed by intraclass correlation coefficient (ICC) determination. Group comparisons were performed by Student’s *t*-test and Fisher’s exact test, when appropriate. Two-tailed *P* value  $<0.05$  was used to establish statistical significance. MedCalc

software was used in all statistical analyses (MedCalc, Inc., Mariakerke, Belgium).

## Results

### Clinical and 2D Doppler echocardiographic data

Mean systolic and diastolic blood pressure ( $124.2 \pm 3.5$  vs.  $123.5 \pm 2.9$  mmHg, *P*= ns), heart rate ( $72 \pm 7$  vs.  $77 \pm 8$  bpm, *P*= ns) and cardiac output ( $5.9 \pm 0.6$  vs.  $5.6 \pm 0.6$  L/min, *P*= ns) did not show significant difference between patients with hemophilia and controls. Routine 2D echocardiographic data did not differ either (*Table 1*). None of the patients and controls showed  $\geq$  grade 1 valvular regurgitations or had valvular stenoses.

### 3DSTE data

In one subject, the near absence of LV twist called as LV-RBR could be detected, data of this subject was managed separately. While apical LV rotation was 3.65 degrees, basal LV rotation proved to be 3.57 degrees leading to 0.08-degree LV apico-basal gradient suggesting counterclockwise LV-RBR (*Figure 2*). In the remaining 13 patients, both LV apical rotation ( $7.25 \pm 6.20$  vs.  $10.07 \pm 3.92$  degrees, *P* $<0.02$ ) and LV twist ( $10.24 \pm 5.60$  vs.  $14.41 \pm 4.26$  degrees, *P* $<0.003$ ) showed significant impairment in patients with hemophilia (*Table 2*).

### Reproducibility of 3DSTE-derived LV rotational parameters

Intraobserver ICCs were 0.86, 0.81 and 0.82 for basal and apical LV rotations and LV twist, respectively. Interobserver ICCs proved to be 0.83, 0.78, and 0.80 for the same parameters, respectively.

## Discussion

3DSTE is one of the most recent developments in cardiovascular imaging with capability of virtual 3D-model-based volumetric and functional assessment of heart chambers and valvular annuli (11,15,16). It provides a non-invasive, fast and easy-to-learn opportunity to perform 3D analysis of the atria and ventricles. While mathematical formulas are used for LV measurements during M-mode and 2D echocardiography, an accurate 3D cast of the LV is created in the course of ECG-gated 3D endocardial

**Table 1** Two-dimensional echocardiographic data of hemophilia patients and controls

Parameters	Controls	Hemophilia patients
LA diameter (mm)	39.8±4.2	38.5±3.4
LV end-diastolic diameter (mm)	48.4±4.0	50.5±3.2
LV end-diastolic volume (mL)	112.0±24.0	123.0±18.6
LV end-systolic diameter (mm)	32.3±2.7	31.9±3.0
LV end-systolic volume (mL)	39.3±8.1	41.3±9.7
LV stroke volume (mL)	73.2±7.9	82.1±9.5
Interventricular septum (mm)	9.6 ±1.2	9.9±1.0
LV posterior wall (mm)	9.5±1.1	9.8±1.0
LV length (mm)	9.4±1.6	9.3±1.7
Relative wall thickness (mm)	0.39±0.06	0.39±0.06
LV ejection fraction (%)	64.7±3.3	66.7±3.9
E (cm/s)	70.4±19.6	72.6±14.5
A (cm/s)	61.2±15.7	66.3±13.2
E/A	1.20±0.36	1.05±0.29

\*, P<0.05 vs. controls. LA, left atrium; LV, left ventricular; E, XXXX; A, XXXX.

**Table 2** Three-dimensional speckle-tracking echocardiography-derived left ventricular volumetric and rotational parameters in hemophilia patients and healthy controls

Parameters	Controls	Hemophilia patients without LV-RBR
Left ventricular volumetric parameters		
LV-EDV (mL)	86.9±29.6	81.6±23.9
LV-ESV (mL)	39.9±11.4	39.1±4.1
LV-EF (%)	56.5±5.6	51.9±4.1*
Left ventricular rotational parameters		
Basal LV rotation (degree)	-3.99±2.20	-2.99±2.16
Apical LV rotation (degree)	10.39±4.16	7.25±6.20*
LV twist (degree)	14.38±3.93	10.24±5.60*
Time of peak LV twist (ms)	303±61	412±181
LV longitudinal strain (%)	-15.8±2.1	-15.3±3.8

\*, P<0.05 vs. controls. EDV, end-diastolic volume; ESV, end-systolic volume; EF, ejection fraction; LV, left ventricular; RBR, rigid body rotation.

tracking during 3DSTE leading to a true volumetric chamber quantification (17). It is known that 3DSTE-derived LVEF is somewhat lower compared to M-mode or 2D echocardiography-derived values due to underestimated LV volumetric parameters, where EDV is more affected

than ESV resulting in a lower 3DSTE-derived LVEF (18,19). Over volumetric measurements, quantitative features of contractility of heart chamber walls represented by LV strains could also be measured in certain directions (radial, longitudinal and circumferential) in the 3D space

223 using the same LV cast (11,15-17).

224 Moreover, there is a complex movement of the LV  
 225 during the cardiac cycle called LV rotational mechanics,  
 226 which could be analysed in detail by the recently developed  
 227 3DSTE. In general, the base of the LV rotates in clockwise  
 228 direction, while the LV apex rotates in counterclockwise  
 229 direction in systole, which is followed by rapid untwisting in  
 230 diastole in normal circumstances (9,10). This sort of special  
 231 and sensitive “towel-wringing”-like LV motion is called LV  
 232 twist and it is responsible for remarkable part of the ejection.  
 233 Physiologically, it is based on the helical arrangement of the  
 234 myocardial fibers: while subendocardial myocardial fibers  
 235 are right-handed, subepicardial ones are left-handed with  
 236 dominant effects on LV rotational mechanics due to their  
 237 larger radius (9,10). LV rotational mechanics seem to be  
 238 sensitive movement that are affected by aortic elasticity and  
 239 stiffness, balance of contraction of subendocardium and  
 240 subepicardium, orientation of myocardial fibers and degree  
 241 of myocardial contraction and relaxation even in healthy  
 242 subjects (9,13). Calculation of 2D echocardiography-derived  
 243 LV twist is not suggested by the most recent guidelines due  
 244 to the fact, that LV twisting mechanism is a 3D motion of  
 245 the LV, therefore its 2D projected measurement would be  
 246 far from the reality (9,20). Therefore, 3DSTE, which is  
 247 able to measure the exact degrees of LV rotation of each  
 248 LV segments/regions and global LV twist from a single  
 249 acquisition, seems to be the optimal solution.

250 The most important finding of the present study is that  
 251 significant 3DSTE-derived LV rotational abnormalities  
 252 could be demonstrated in patients with hemophilia.  
 253 Although a small number of patients were examined,  
 254 reduced apical LV rotation and twist were found in  
 255 hemophilia. Moreover, one patient showed LV-RBR.  
 256 The correct explanation is not obvious, but decreased LV  
 257 twist and apical rotation should be considered as a fine  
 258 compensational mechanism related to haemophilia-related  
 259 haemostatic changes and related alterations in wall stress/  
 260 shear stress. It is strengthened by a recent study from  
 261 the MAGYAR-Path Study, where only certain regional  
 262 LV circumferential strains (CSs) proved to be reduced in  
 263 haemophilia, global and mean segmental LV strains and  
 264 other regional LV strains did not differ between patients  
 265 with haemophilia and matched controls (21). Due to known  
 266 relationship between LV-CS and LV twist, fine settings of  
 267 LV mechanics via LV apical rotation could be theorized  
 268 due these abnormalities in haemophilia. However, other  
 269 factors like vascular functional alterations, the effects of  
 270 concomitant cardiovascular risk factors, or other factors

could also not be excluded (4,8,22). According to recent 271  
 findings, hypertension was found to be a frequent finding 272  
 in hemophilia with some increase in septal thickness and 273  
 changes in diastolic function (23). Forty-three percent 274  
 of our patients had hypertension, which is known to 275  
 be associated with increased LV twist, which further 276  
 strengthen our theories (24). In a recent study, children 277  
 with severe hemophilia A showed higher arterial stiffness, 278  
 and myocardial performance index, whereas the ejection 279  
 time was shorter than in the control group (22). Similar 280  
 alterations in LV rotational mechanics could be detected 281  
 in other hematological disorders as well including 282  
 hypereosinophilic syndrome and amyloidosis with larger 283  
 ratio of patients with LV-RBR (25,26). However, further 284  
 studies are warranted in a larger patient population to 285  
 confirm our findings. 286

### 287 288 Limitation section

289 The following important limitations should be considered 290  
 when interpreting the results. Hemophilia is a rare disease, 291  
 therefore only limited number of patients could be collected 292  
 and involved in the study from the tertiary center for patients 293  
 with hematological disorders of our university responsible 294  
 for the treatment of South-East Hungary. The present study 295  
 aimed to analyse 3DSTE-derived LV rotational mechanics 296  
 in hemophilia. Neither chambers other than the LV, nor LV 297  
 strains featuring LV contractility were aimed to be assessed 298  
 by 3DSTE (11). Several technical limitations are known to 299  
 affect 3DSTE including low temporal and spatial resolution, 300  
 which could affect the measurements (11,15,16). Some adult 301  
 hemophilia patients had risk factors, which could affect 302  
 the results. Hemophilia patients were treated with factor 303  
 replacement therapy to prevent bleeding, which could 304  
 theoretically affect the findings. 305

### 306 307 Conclusions

308 LV rotational abnormalities are present in hemophilia with 309  
 reduced LV apical rotation and twist. 310

### 311 312 Acknowledgments

313 *Funding:* None. 314

### 315 316 Footnote

317 *Conflicts of Interest:* All authors have completed the ICMJE 318



uniform disclosure form (available at <https://dx.doi.org/10.21037/qims-21-30>). Dr. AN serves as an unpaid editorial board member of *Quantitative Imaging in Medicine and Surgery*. The authors have no conflicts of interest to declare.

**Ethical Statement:** The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by institutional ethics committee of the University of Szeged (NO.: 71/2011) and informed consent was taken from all the patients.

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